EMPAVELI- pegcetacoplan injection, solution
Apellis Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EMPAVELI safely and effectively. See full prescribing information for EMPAVELI.
EMPAVELI™ (pegcetacoplan) injection, for subcutaneous use
Initial U.S. Approval: 2021

-------------- **INDICATIONS AND USAGE** -------------------
EMPAVELI is a complement inhibitor indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). (1) (1)

------------------ **DOSAGE AND ADMINISTRATION** -------------
- Recommended dosage is 1,080 mg by subcutaneous infusion twice weekly via a commercially available pump. (2.2)
- See Full Prescribing Information for instructions on preparation and administration. (2.2, 2.3)

------------------ **DOSAGE FORMS AND STRENGTHS** -------------
- Injection: 1,080 mg/20 mL (54 mg/mL) in a single-dose vial. (3)

---------------------- **CONTRAINDICATIONS** -----------------
EMPAVELI is contraindicated in: (4)
- Patients with hypersensitivity to pegcetacoplan or any of the excipients. (4)
- Patients who are not currently vaccinated against certain encapsulated bacteria unless the risks of delaying EMPAVELI treatment outweigh the risks of developing a serious bacterial infection with an encapsulated organism. (4, 5.1)
- Patients with unresolved serious infection caused by encapsulated bacteria. (4)

----------------- **WARNINGS AND PRECAUTIONS** -----------------
Use caution when administering EMPAVELI to patients with: (5)

- Serious infections caused by encapsulated bacteria. (5.1)
- Infusion-Related Reactions: Monitor patients for infusion-related reactions and institute appropriate medical management as needed. (5.3)
- Interference with Laboratory Tests: Use of silica reagents in coagulation panels may result in artificially prolonged activated partial thromboplastin time (aPTT). (5.5)

--**ADVERSE REACTIONS**--

Most common adverse reactions in patients with PNH (incidence ≥10%) were injection-site reactions, infections, diarrhea, abdominal pain, respiratory tract infection, viral infection, and fatigue. (6.1) (6) (6)

To report SUSPECTED ADVERSE REACTIONS, contact Apellis Pharmaceuticals, Inc. at 1-833-866-3346 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)

Revised: 5/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS CAUSED BY ENCAPSULATED BACTERIA

Meningococcal infections may occur in patients treated with EMPAVELI and may become rapidly life threatening or fatal if not recognized and treated early. Use of EMPAVELI may predispose individuals to serious infections, especially those caused by encapsulated bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B [see Warnings and Precautions (5.1)].

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria in patients with altered immunocompetence associated with complement deficiencies.**
- **Vaccinate patients against encapsulated bacteria as recommended at least 2 weeks prior to administering the first dose of EMPAVELI unless the risks of delaying therapy with EMPAVELI outweigh the risk of developing a serious infection. *See Warnings and Precautions (5.1)* for additional guidance on the management of the risk of serious infections.**
- **Vaccination reduces, but does not eliminate, the risk of serious infections. Monitor patients for early signs of serious infections and evaluate immediately if infection is suspected.**

EMPAVELI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the EMPAVELI REMS, prescribers must enroll in the program [see Warnings and Precautions (5.2)]. Enrollment in the EMPAVELI REMS program and additional information are available by telephone: 1-888-343-7073 or at www.empavelirems.com .

EMPAVELI ™ is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

2.1 Recommended Vaccination and Prophylaxis

Vaccinate patients against encapsulated bacteria, including *Streptococcus pneumoniae* , *Neisseria meningitidis* , and *Haemophilus influenzae* type B at least 2 weeks prior to initiation of EMPAVELI therapy according to current ACIP guidelines *[see Warnings and Precautions (5.1)]* .

Provide 2 weeks of antibacterial drug prophylaxis to patients if EMPAVELI must be initiated immediately and vaccines are administered less than 2 weeks before starting therapy with EMPAVELI.

Healthcare professionals who prescribe EMPAVELI must enroll in the REMS for EMPAVELI *[see Warnings and Precautions (5.2)]*.

2.2 Dosage

The recommended dose of EMPAVELI is 1,080 mg by subcutaneous infusion twice weekly via a commercially available infusion pump with a reservoir of 20 mL.

Dosage for patients switching to EMPAVELI from C5 inhibitors

To reduce the risk of hemolysis with abrupt treatment discontinuation:
- For patients switching from eculizumab, initiate EMPAVELI while continuing eculizumab at its current dose. After 4 weeks, discontinue eculizumab before continuing on monotherapy with EMPAVELI.
- For patients switching from ravulizumab, initiate EMPAVELI no more than 4 weeks after the last dose of ravulizumab.

Dose Adjustment
- For lactate dehydrogenase (LDH) levels greater than 2 × the upper limit of normal (ULN), adjust the dosing regimen to 1,080 mg every three days.
- In the event of a dose increase, monitor LDH twice weekly for at least 4 weeks.

Missed Dose
- Administer EMPAVELI as soon as possible after a missed dose. Resume the regular dosing schedule following administration of the missed dose.
  2.3 Administration
  EMPAVELI is for subcutaneous infusion using an infusion pump.
  EMPAVELI is intended for use under the guidance of a healthcare professional. After proper training in subcutaneous infusion, a patient may self-administer, or the patient's caregiver may administer EMPAVELI, if a healthcare provider determines that it is appropriate.
- Refer to the EMPAVELI Instructions for Use and the infusion pump manufacturer's instructions for full preparation and administration information.
- Use aseptic technique when preparing and administering EMPAVELI.
- Prior to use, allow EMPAVELI to reach room temperature for approximately 30 minutes. Keep the vial in the carton until ready for use to protect from light.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. EMPAVELI is a clear, colorless to slightly yellowish solution. Do not use if the liquid looks cloudy, contains particles, or is dark yellow.
- Use a needleless transfer device (such as a vial adapter) or a transfer needle to fill the syringe.
- Rotate infusion sites (i.e., abdomen, thighs, hips, upper arms) from one infusion to the next. Do not infuse where the skin is tender, bruised, red, or hard. Avoid infusing into tattoos, scars, or stretch marks.
- If multi-infusion sets are needed, ensure the infusion sites are at least 3 inches apart.
- The typical infusion time is approximately 30 minutes (if using two infusion sites) or approximately 60 minutes (if using one infusion site).
- Discard any unused portion.

- Injection: 1,080 mg/20 mL (54 mg/mL) in a single-dose vial. (3)

EMPAVELI is contraindicated in:
- Patients with hypersensitivity to pegcetacoplan or to any of the excipients.
- Patients who are not currently vaccinated against certain encapsulated bacteria, unless the risks of delaying EMPAVELI treatment outweigh the risks of developing a bacterial infection with an encapsulated organism [see Warnings and Precautions (5.1)].
- Patients with unresolved serious infection caused by encapsulated bacteria including

Streptococcus pneumoniae, *Neisseria meningitidis*, and *Haemophilus influenzae*.

5.1 Serious Infections Caused by Encapsulated Bacteria

The use of EMPAVELI may predispose individuals to serious, life-threatening, or fatal infections caused by encapsulated bacteria including *Streptococcus pneumoniae* , *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B (Hib). To reduce the risk of infection, all patients must be vaccinated against these bacteria according to the most current ACIP recommendations for patients with altered immunocompetence associated with complement deficiencies. Revaccinate patients in accordance with ACIP recommendations considering the duration of therapy with EMPAVELI.

For patients without known history of vaccination, administer required vaccines at least 2 weeks prior to receiving the first dose of EMPAVELI. If immediate therapy with EMPAVELI is indicated, administer required vaccine as soon as possible and provide patients with 2 weeks of antibacterial drug prophylaxis.

Closely monitor patients for early signs and symptoms of serious infection and evaluate patients immediately if an infection is suspected. Promptly treat known infections. Serious infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider discontinuation of EMPAVELI in patients who are undergoing treatment for serious infections.

5.2 EMPAVELI REMS

Because of the risk of serious infections, EMPAVELI is available only through a restricted program under a REMS. Under the EMPAVELI REMS, prescribers must enroll in the program.

Prescribers must counsel patients about the risk of serious infection, provide the patients with the REMS educational materials, and ensure patients are vaccinated against encapsulated bacteria.

Enrollment in the EMPAVELI REMS and additional information are available by telephone: 1-888-343-7073 or at www.empavelirems.com.

5.3 Infusion-Related Reactions

Systemic hypersensitivity reactions (e.g., facial swelling, rash, urticaria) have occurred in patients treated with EMPAVELI. One patient (less than 1% in clinical studies) experienced a serious allergic reaction which resolved after treatment with antihistamines. If a severe hypersensitivity reaction (including anaphylaxis) occurs, discontinue EMPAVELI infusion immediately, institute appropriate treatment, per standard of care, and monitor until signs and symptoms are resolved.

5.4 Monitoring PNH Manifestations after Discontinuation of EMPAVELI

After discontinuing treatment with EMPAVELI, closely monitor for signs and symptoms of hemolysis, identified by elevated LDH levels along with sudden decrease in PNH clone size or hemoglobin, or reappearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, dyspnea, major adverse vascular events (including thrombosis), dysphagia, or erectile dysfunction. Monitor any patient who discontinues EMPAVELI for at least 8 weeks to detect hemolysis and other reactions. If hemolysis, including elevated LDH, occurs after discontinuation of EMPAVELI, consider restarting treatment with

EMPAVELI.

5.5 Interference with Laboratory Tests

There may be interference between silica reagents in coagulation panels and EMPAVELI that results in artificially prolonged activated partial thromboplastin time (aPTT); therefore, avoid the use of silica reagents in coagulation panels.

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:
- Serious Infections Caused by Encapsulated Bacteria [see Warnings and Precautions (5.1)]
- Infusion-Related Reactions [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Paroxysmal Nocturnal Hemoglobinuria

The data described below reflect the exposure of EMPAVELI in 80 adult patients with PNH who received EMPAVELI (n=41) or eculizumab (n=39) at the recommended dosing regimens for 16 weeks. Serious adverse events were reported in 7 (17%) patients with PNH receiving EMPAVELI. The most common serious adverse reaction in patients treated with EMPAVELI was infections (5%). The most common adverse reactions (≥10%) with EMPAVELI were injection-site reactions, infections, diarrhea, abdominal pain, respiratory tract infection, viral infection, and fatigue.

Table 1 describes the adverse reactions that occurred in ≥5% of patients treated with EMPAVELI in Study APL2-302.

Table 1: Adverse Reactions Reported in >5% Patients Treated with EMPAVELI

Adverse Reaction	EMPAVELI (N=41) n (%)	Eculizumab (N=39) n (%)
General disorders and administration site conditions		
Injection-site reaction*	16 (39)	2 (5)
Fatigue*	5 (12)	9 (23)
Chest pain*	3 (7)	1 (3)
Infections and infestations		
Infections*	12 (29)	10 (26)
Respiratory tract infection*	6 (15)	5 (13)
Viral Infection*	5 (12)	3 (8)
Gastrointestinal disorders		
Diarrhea	9 (22)	1 (3)
Abdominal pain*	8 (20)	4 (10)
Musculoskeletal disorders		
Back pain*	3 (7)	4 (10)
Nervous system disorders		

Headache	3 (7)	9 (23)
Vascular disorders		
Systemic hypertension*	3 (7)	1 (3)

*The following terms were combined:

Abdominal pain includes: abdominal pain upper, abdominal discomfort, abdominal pain, abdominal pain lower, abdominal tenderness, epigastric discomfort

Back pain includes: back pain, sciatica

Chest pain includes: chest discomfort, non-cardiac chest pain, musculoskeletal chest pain, chest pain

Fatigue includes: asthenia, lethargy, fatigue

Infections include: oral herpes, bacterial infection, fungal infection, gastrointestinal infection, gastrointestinal viral infection, influenza-like illness, nasopharyngitis, pulpitis dental, rhinitis, tonsillitis, tonsillitis bacterial, vulvovaginal mycotic infection, hordeolum, sepsis, furuncle, otitis externa, viral respiratory tract infection, gastroenteritis, upper respiratory tract infection, bronchitis, ear infection, respiratory tract infection, rhinovirus infection, sinusitis, urinary tract infection

Injection-site reaction includes: injection-site erythema, injection-site reaction, injection-site swelling, injection-site induration, injection-site bruising, injection-site pain, injection-site pruritus, vaccination-site reaction, administration-site swelling, injection-site hemorrhage, injection-site edema, injection-site warmth, administration-site pain, application-site pain, injection-site mass, injection-site rash, vaccination-site pain

Respiratory tract infection includes: influenza-like illness, nasopharyngitis, rhinitis, tonsillitis, viral upper respiratory tract infection, upper respiratory tract infection, respiratory tract infection, sinusitis

Systemic hypertension includes: hypertension

Viral infection includes: oral herpes, gastrointestinal viral infection, viral upper respiratory tract infection, rhinovirus infection

Clinically relevant adverse reactions in less than 5% of patients include:
- Intestinal ischemia
- Biliary sepsis
- Hypersensitivity pneumonitis

Description of Select Adverse Reactions

Injection-Site Reactions

Injection/infusion-site reactions (e.g., erythema, swelling, induration, pruritis, and pain) have been reported during Study APL2-302. These reactions were mild or moderate in severity.

Diarrhea

Nine cases of diarrhea have been reported during Study APL2-302. All cases were mild.

6.2 mmunogenicity

As with all therapeutic peptides, there is a potential for immunogenicity. Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. The available methodology and data on anti-pegcetacoplan antibody formation were not adequate to fully assess the incidence of anti-drug antibodies or their effect on pharmacokinetics, pharmacodynamics, safety, or effectiveness of pegcetacoplan.

8.1 Pregnancy

Risk Summary

There are insufficient data on EMPAVELI use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with untreated PNH in pregnancy *(see Clinical Considerations)*. The use of EMPAVELI may be considered following an assessment of the risks and benefits.

Treatment of pregnant cynomolgus monkeys with pegcetacoplan at a subcutaneous dose of 28 mg/kg/day (2.9 times human exposure based on AUC) from the gestation period through parturition resulted in a statistically significant increase in abortions or stillbirths compared to controls *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of major birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or fetal/neonatal risk

PNH in pregnancy is associated with adverse maternal outcomes, including worsening cytopenias, thrombotic events, infections, bleeding, miscarriages and increased maternal mortality, and adverse fetal outcomes, including fetal death and premature delivery.

Data

Animal Data

Animal reproduction studies with pegcetacoplan were conducted in cynomolgus monkeys. Pegcetacoplan treatment of pregnant cynomolgus monkeys at a subcutaneous dose of 28 mg/kg/day (2.9 times human exposure based on AUC) from the gestation period through parturition resulted in a statistically significant increase in abortions and stillbirths compared to controls. No increase in abortions or stillbirths occurred at a dose of 7 mg/kg/day (1.3 times human exposure based on AUC). No maternal toxicity or teratogenic effects were observed in offspring delivered at term. No developmental effects were observed in infants up to 6 months postpartum. Systemic exposure to pegcetacoplan of less than 1% of maternal levels was detected in fetuses from monkeys treated with 28 mg/kg/day from the period of organogenesis through the second trimester.

8.2 Lactation

Risk Summary

It is not known whether pegcetacoplan is secreted in human milk or whether there is

potential for absorption and harm to the infant. There are no data on the effects of pegcetacoplan on milk production. Pegcetacoplan is present in milk of lactating monkeys *see Animal Data)* . Since many medicinal products are secreted into human milk, and because of the potential for serious adverse reaction in a breastfeeding child, breastfeeding should be discontinued during treatment and for 40 days after the last dose.

Data

Animal Data

Pegcetacoplan was detectable in milk of lactating monkeys at less than 1% concentration of serum levels but was not detectable in the serum of nursing infants.

8.3 Females and Males of Reproductive Potential

Contraception

Females

EMPAVELI may cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Pregnancy testing is recommended for females of reproductive potential prior to treatment with EMPAVELI. Advise female patients of reproductive potential to use effective contraception during treatment with EMPAVELI and for 40 days after the last dose.

8.4 Pediatric Use

Safety and effectiveness have not been established.

8.5 Geriatric Use

Clinical studies of EMPAVELI did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between geriatric and younger patients.

EMPAVELI contains pegcetacoplan, a complement inhibitor. Pegcetacoplan is a symmetrical molecule comprised of two identical pentadecapeptides covalently bound to the ends of a linear 40-kiloDalton (kDa) PEG molecule. The peptide portions of pegcetacoplan contain 1-methyl-L-tryptophan (Trp(Me)) in position 4 and amino(ethoxyethoxy)acetic acid (AEEA) in position 14.

The molecular weight of pegcetacoplan is approximately 43.5 kDa. The molecular formula is $C_{1970}H_{3848}N_{50}O_{947}S_4$. The structure of pegcetacoplan is shown below.
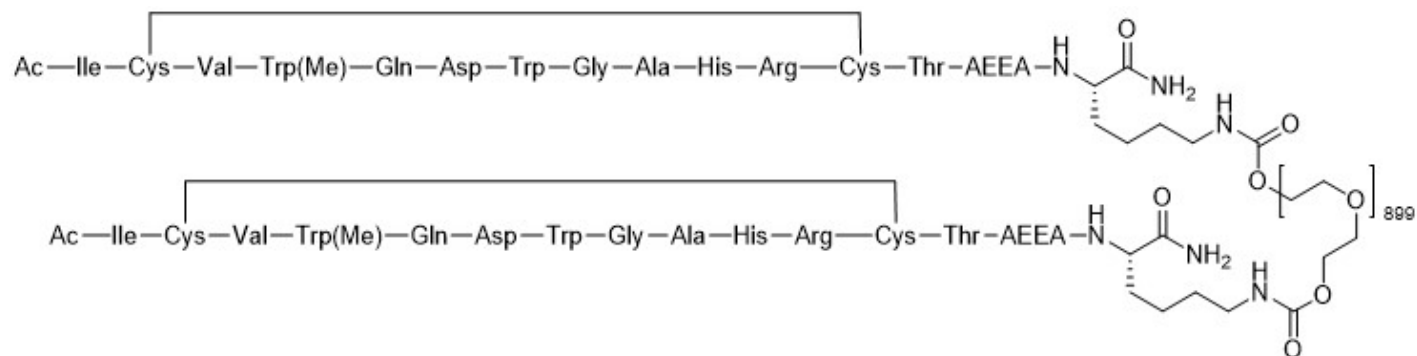
EMPAVELI injection is a sterile, clear, colorless to slightly yellowish aqueous solution for

subcutaneous use and is supplied in a 20-mL single-dose vial. Each 1 mL of solution contains 54 mg of pegcetacoplan, 41 mg of sorbitol, 0.384 mg of glacial acetic acid, 0.490 mg of sodium acetate trihydrate, and Water for Injection USP. EMPAVELI may also contain sodium hydroxide and/or additional glacial acetic acid for adjustment to a target pH of 5.0.

12.1 Mechanism of Action

Pegcetacoplan binds to complement protein C3 and its activation fragment C3b, thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation. In PNH, extravascular hemolysis (EVH) is facilitated by C3b opsonization while intravascular hemolysis (IVH) is mediated by the downstream membrane attack complex (MAC). Pegcetacoplan acts proximally in the complement cascade controlling both C3b-mediated EVH and terminal complement-mediated IVH.

12.2 Pharmacodynamics

The mean C3 concentration increased from 0.94 g/L at baseline to 3.83 g/L at Week 16 in patients with PNH administered multiple doses of pegcetacoplan. The baseline percentage of PNH Type II + III RBCs was 66.8%, which increased to 93.9% at Week 16. The mean percentage of PNH Type II + III RBCs with C3 deposition was 17.7% at baseline and decreased to 0.20% at Week 16.

Cardiac Electrophysiology

At the recommended dose of EMPAVELI, no large mean increases in QTc interval (i.e., greater than 20 msec) were observed.

12.3 Pharmacokinetics

Steady-state serum pegcetacoplan concentrations were achieved approximately 4 to 6 weeks following the first dose and mean (%CV) steady-state trough serum concentrations ranged between 655 (18.6%) to 706 (15.1%) mcg/mL in patients with PNH treated for 16 weeks. Exposure of pegcetacoplan increases proportionally over a dosage range from 45 to 1,440 mg (0.04 to 1.33 times the approved recommended dose).

Absorption

The median T_{max} of pegcetacoplan is between 108 and 144 hours (4.5 to 6.0 days).

Distribution

The mean (%CV) volume of distribution of pegcetacoplan is approximately 3.9 L (35%) in patients with PNH.

Elimination

The estimated mean (CV%) of clearance (CL) is 0.37 L/day (28%) and median effective half-life of elimination ($t_{1/2}$) is 8.0 days in patients with PNH.

Metabolism

Pegcetacoplan is expected to be metabolized into small peptides and amino acids by catabolic pathways.

Specific Populations

There were no clinically significant differences on the pharmacokinetics of pegcetacoplan

based on age (19 to 81 years old), sex, race (Asian vs. non-Asian), renal impairment, and hepatic function as evaluated by total bilirubin (0.3-4.3 mg/dL), albumin (3.6-4.9 g/dL), aspartate aminotransferase (13-116 IU/L), or alanine aminotransferase (9-61 IU/L).

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal carcinogenicity studies of pegcetacoplan have not been conducted.

Pegcetacoplan was not mutagenic when tested in an *in vitro* bacterial reverse mutation (Ames) and was not genotoxic in an *in vitro* assay in human TK6 cells or in an *in vivo* micronucleus assay in mice.

Effects of pegcetacoplan on fertility have not been studied in animals. There were no microscopic abnormalities in male or female reproductive organs in toxicity studies in rabbits and monkeys.

13.2 Animal Toxicology and/or Pharmacology

In toxicology studies in rabbits and cynomolgus monkeys, epithelial vacuolation and infiltrates of vacuolated macrophages were observed in multiple tissues, including the renal tubules, following daily subcutaneous doses of pegcetacoplan up to 7 times the human dose. These findings are attributable to uptake of the PEG moieties of pegcetacoplan. Renal degeneration was observed microscopically in rabbits at exposures (C_{max} and AUC) less than those for the human dose, and in monkeys at exposures approximately 2.7-fold those for the human dose. The clinical significance of these findings is uncertain.

14.1 Paroxysmal Nocturnal Hemoglobinuria

The efficacy and safety of EMPAVELI in patients with PNH were assessed in a randomized, open-label, active comparator-controlled, 16-week Phase 3 study (Study APL2-302; NCT03500549). The study enrolled patients with PNH who had been treated with a stable dose of eculizumab for at least the previous 3 months and with Hb levels less than 10.5 g/dL.

Eligible patients entered a 4-week run-in period during which they received EMPAVELI 1,080 mg subcutaneously twice weekly in addition to their current dose of eculizumab. Patients were then randomized in a 1:1 ratio to receive either 1,080 mg of EMPAVELI twice weekly or their current dose of eculizumab through the duration of the 16-week randomized controlled period (RCP). If required, the dose of EMPAVELI could be adjusted to 1,080 mg every 3 days. EMPAVELI was administered as a subcutaneous infusion; the infusion time was approximately 20 to 40 minutes.

Randomization was stratified based on the number of packed red blood cell (PRBC) transfusions within the 12 months prior to Day -28 (<4; ≥4) and platelet count at screening (<100,000/mm^3; ≥100,000/mm^3). Following completion of the RCP, all patients entered a 32-week open-label period and received monotherapy with EMPAVELI. All patients who completed the 48-week period were eligible to enroll in a separate long-term extension study.

Patients were vaccinated against *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B (Hib), either within 2 years prior to Day 1 or within 2 weeks after starting treatment with EMPAVELI. Patients vaccinated after initiation of treatment with EMPAVELI received prophylactic treatment

with appropriate antibiotics until 2 weeks after vaccination. In addition, prophylactic antibiotic therapy was administered at the discretion of the investigator in accordance with local treatment guidelines for patients with PNH receiving treatment with a complement inhibitor.

A total of 80 patients were randomized to receive treatment, 41 to EMPAVELI and 39 to eculizumab. Demographics and baseline disease characteristics were generally well balanced between treatment groups (see Table 2). The median times from PNH diagnosis to Day -28 were 6.0 and 9.7 years, respectively, for EMPAVELI and eculizumab. The baseline mean total PNH RBC clone sizes (Type III) were 47% for EMPAVELI and 50% for eculizumab. Twenty-nine percent and 23% of patients had a history of major adverse vascular events, and 37% and 26% had a history of thrombosis for patients receiving EMPAVELI or eculizumab, respectively. Within 28 days prior to the first dose of EMPAVELI or eculizumab, respectively, 34% and 31% of subjects used anti-thrombotic agents (anti-platelet and/or anticoagulants). During Study APL2-302, 37% and 36% of subjects on EMPAVELI and eculizumab, respectively, used antithrombotic agents. A total of 38 patients in the group treated with EMPAVELI and 39 patients in the eculizumab group completed the 16-week RCP and continued into the 32-week open-label period. Because of adverse events of hemolysis, 3 patients were discontinued from the EMPAVELI group during the RCP. Two out of 41 patients in the EMPAVELI group needed the dose adjustment to 1,080 mg every 3 days.

Table 2: Patient Baseline Demographics and Characteristics in Study APL2-302

Parameter	Statistics	EMPAVELI (n=41)	Eculizumab (n=39)
Age (years)	Mean (SD)	50.2 (16.3)	47.3 (15.8)
Sex Female	n (%)	27 (65.9)	22 (56.4)
Race Asian Black or African American White Other Not reported	n (%) n (%) n (%) n (%) n (%)	5 (12.2) 2 (4.9) 24 (58.5) 0 10 (24.4)	7 (17.9) 0 25 (64.1) 1 (2.6) 6 (15.4)
Ethnicity Hispanic or Latino Not Hispanic or Latino Not reported	n (%) n (%) n (%)	2 (4.9) 29 (70.7) 10 (24.4)	1 (2.6) 32 (82.1) 6 (15.4)
Hemoglobin level (g/dL)	Mean (SD)	8.7 (1.1)	8.7 (0.9)
Absolute reticulocyte count (10^9 cells/L)	Mean (SD)	218 (75.0)	216 (69.1)
LDH level (U/L)	Mean (SD)	257.5 (97.7)	308.6 (284.8)
Number of transfusions in last 12 months prior to Day -28	Mean (SD)	6.1 (7.3)	6.9 (7.7)
<4	n (%)	20 (48.8)	16 (41.0)
≥4	n (%)	21 (51.2)	23 (59.0)

The efficacy of EMPAVELI was based on change from baseline to Week 16 (during RCP) in hemoglobin level. Baseline was defined as the average of measurements recorded

prior to taking the first dose of EMPAVELI. Supportive efficacy data included transfusion avoidance, defined as the proportion of patients who did not require a transfusion during the RCP, and change from baseline to Week 16 in absolute reticulocyte count (ARC).

EMPAVELI was superior to eculizumab for the change from baseline in hemoglobin level at Week 16 (*P*<0.0001). The adjusted mean change from baseline in hemoglobin level was 2.37 g/dL in the group treated with EMPAVELI versus -1.47 g/dL in the eculizumab group (Figure 1), demonstrating an adjusted mean increase of 3.84 g/dL with EMPAVELI compared to eculizumab at Week 16 (95% CI, 2.33-5.34).

Figure 1: Adjusted Mean (± SE) Change from Baseline to Week 16 in Hemoglobin (g/dL)*
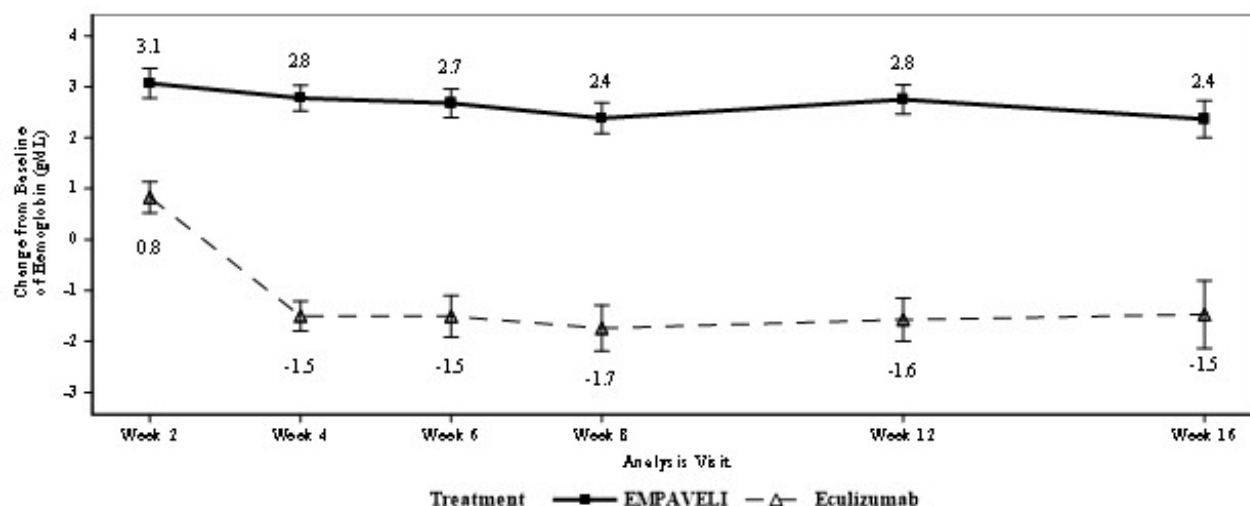
*Treatment effect estimates from a mixed model are shown. The mixed model contained the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.

Non-inferiority was demonstrated in the endpoints of transfusion avoidance and change from baseline in ARC.

The adjusted means, treatment differences, and confidence intervals (CIs) for additional efficacy results are shown in Table 3.

Table 3: Additional Efficacy Results

	EMPAVELI (n=41)	Eculizumab (n=39)	Difference (95% CI)
Transfusion avoidance, n (%)	35 (85%)	6 (15%)	63%* (48%, 77%)
Change from baseline in ARC (10^9 cells/L), LS [†] mean (SE) [‡]	-136 (6.5)	28 (11.9)	-164 (-189.9, -137.3)

*Difference in percentages and 95% CI were based on the stratified Miettinen–Nurminen method.

†LS = Least square

‡SE = Standard error

Efficacy was generally similar across subgroups based on sex, race, and age.

The results of the controlled trial of EMPAVELI in patients with PNH are supported by 2 uncontrolled studies in patients with PNH who were not receiving a complement inhibitor: Study APL2-202 (NCT03593200) and Study APL2-CP-PNH-204 (NCT02588833). These studies enrolled a total of 24 patients with PNH who had a PNH clone size of at least 10%, an LDH at least 2 times the upper limit of normal, and at least 1 transfusion in the 12 months prior to enrollment. In both studies, the treatment duration was approximately 1 year. Increases in hemoglobin were observed in these trials.

How Supplied

EMPAVELI injection is a clear, colorless to slightly yellowish aqueous solution for subcutaneous infusion supplied as 1,080 mg/20 mL (54 mg/mL) solution in 20-mL single-dose vials.

EMPAVELI is available in 20-mL single-dose vials individually packaged in cartons that are supplied in 8-count convenience cartons. NDC 73606-010-01.

Storage and Handling

Store vials of EMPAVELI refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not use beyond the expiration date stamped on the carton.

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Serious Infections Caused by Encapsulated Bacteria

Advise patients of the risk of serious infection. Inform patients that they are required to receive vaccinations against encapsulated bacteria at least 2 weeks prior to receiving the first dose of EMPAVELI if they have not been previously vaccinated. They are required to be revaccinated according to current medical guidelines for encapsulated bacteria while on EMPAVELI therapy. Inform patients that vaccination may not prevent serious infection and strongly advise patients to seek immediate medical attention if these signs or symptoms occur. These signs and symptoms include the following:
- fever with or without shivers or the chills
- fever and a rash
- shortness of breath
- extreme pain or discomfort
- headache with nausea or vomiting
- high heart rate
- headache and a fever
- headache with a stiff neck or stiff back
- confusion
- muscle aches with flu-like symptoms
- clammy skin
- eyes sensitive to light

Inform patients that they will be given a Patient Safety Card for EMPAVELI that they should carry with them at all times. This card describes symptoms which, if experienced, should prompt the patient to seek immediate medical evaluation.

<u>Anaphylaxis and infusion-related reactions</u>

Advise patients of the risk of anaphylaxis and infusion-related reactions. Inform patients that anaphylaxis is life-threatening and strongly advise patients to seek immediate medical attention if these signs or symptoms occur. These signs and symptoms include the following:
- difficulty breathing including shortness of breath and wheezing
- swollen tongue or throat
- feeling faint
- rapid heart rate
- skin reactions, including hives and itching
- nausea or vomiting
- confusion and anxiety
- dizziness or fainting

<u>Discontinuation</u>

Inform patients with PNH that they may develop hemolysis due to PNH when EMPAVELI is discontinued and that they will be monitored by their healthcare professional for at least 8 weeks following discontinuation of EMPAVELI.

Inform patients who discontinue EMPAVELI to keep the Patient Safety Card with them for 2 months after the last dose of EMPAVELI, because the increased risk of serious infection persists for several weeks following discontinuation of EMPAVELI.

EMPAVELI™
(pegcetacoplan)

XXXXXXXX SN
MM YYYY Exp
XXXXX XXXXXX Lot

GTIN 00373606010019

NDC 73606-010-01

EMPAVELI™
(pegcetacoplan)
Injection

**1,080 mg/20 mL
(54 mg/mL)**

For Subcutaneous Infusion Only

Dispense the enclosed
Medication Guide to each patient.

One 20 mL Single-Dose Vial.
Discard unused portion.

Rx only   Apellis

Dosage: See prescribing information.

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.

Keep out of reach of children.

REMOVE A SINGLE VIAL CARTON FROM REFRIGERATOR FOR AT LEAST 30 MINUTES PRIOR TO USE. DISCARD UNUSED PORTION.

EACH VIAL CONTAINS: pegcetacoplan (54 mg/mL), sorbitol (41 mg/mL), glacial acetic acid (0.384 mg/mL), sodium acetate trihydrate (0.490 mg/mL), and Water for injection, USP. EMPAVELI may also contain sodium hydroxide and/or additional glacial acetic acid for adjustment to a target pH of 5.0.

NDC 73606-010-01

EMPAVELI™
(pegcetacoplan)
Injection

**1,080 mg/20 mL
(54 mg/mL)**

For Subcutaneous Infusion Only

Dispense the enclosed
Medication Guide to each patient.

One 20 mL Single-Dose Vial.
Discard unused portion.

Rx only   Apellis

Manufactured for
Apellis Pharmaceuticals, Inc.,
100 Fifth Avenue,
Waltham, MA 02451

Product of Switzerland

02607602

3 73606 01001 9

EMPAVELI

pegcetacoplan injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:73606-010
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
PEGCETACOPLAN (UNII: TO3JYR3BOU) (PEGCETACOPLAN - UNII:TO3JYR3BOU)	PEGCETACOPLAN	1080 mg in 20 mL

Product Characteristics

Color	white	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:73606-010-01	1 in 1 CARTON	05/14/2021	
1		20 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA215014	05/14/2021	

Labeler - Apellis Pharmaceuticals, Inc. (961959629)

Registrant - Apellis Pharmaceuticals, Inc. (961959629)

Establishment

Name	Address	ID/FEI	Business Operations
Cangene BioPharma, LLC		050783398	manufacture(73606-010)

Establishment

Name	Address	ID/FEI	Business Operations
AndersonBrecon Inc		053217022	pack(73606-010)

Establishment

Name	Address	ID/FEI	Business Operations
Eurofins Lancaster Laboratories, Inc.		069777290	analysis(73606-010)

Establishment

Name	Address	ID/FEI	Business Operations
Nelson Laboratories, LLC		151663234	analysis(73606-010)

Establishment

Name	Address	ID/FEI	Business Operations
Solvias AG		480739627	analysis(73606-010)

Establishment

Name	Address	ID/FEI	Business Operations
Bachem, AG		482220311	api manufacture(73606-010)

Establishment

Name	Address	ID/FEI	Business Operations
Juzen Chemical Corporation		691036974	manufacture(73606-010)

Establishment

Name	Address	ID/FEI	Business Operations
NOF Corporation		706286887	manufacture(73606-010)

Establishment

Name	Address	ID/FEI	Business Operations
Eurofins Advantar Laboratories, Inc.		849636258	analysis(73606-010)

Establishment

Name	Address	ID/FEI	Business Operations
Apellis Pharmaceuticals, Inc.		961959629	manufacture(73606-010)

Revised: 7/2021   Apellis Pharmaceuticals, Inc.